General

Guideline Title

Selection of optimal adjuvant chemotherapy regimens for human epidermal growth factor receptor 2 (HER2)-negative and adjuvant targeted therapy for HER2-positive breast cancers: an American Society of Clinical Oncology guideline adaptation of the Cancer Care Ontario clinical practice guideline.

Bibliographic Source(s)

Denduluri N, Somerfield MR, Eisen A, Holloway JN, Hurria A, King TA, Lyman GH, Partridge AH, Telli ML, Trudeau ME, Wolff AC. Selection of optimal adjuvant chemotherapy regimens for human epidermal growth factor receptor 2 (HER2)-negative and adjuvant targeted therapy for HER2-positive breast cancers: an American Society of Clinical Oncology guideline adaptation of the Cancer Care Ontario clinical practice guideline. J Clin Oncol. 2016 Jul 10;34(20):2416-27. [32 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

The following sections present the recommendations adapted from the Cancer Care Ontario (CCO) Program in Evidence-based Care guideline on optimal systemic therapy for early female breast cancer. Recommendations identified by an asterisk are taken verbatim from the CCO guideline. Otherwise, recommendations have been substantively adapted or reworded for clarity by the American Society of Clinical Oncology (ASCO) Panel.

Recommendations for Human Epidermal Growth Factor Receptor 2 (HER2)-Negative Breast Cancer

Use of an Anthracycline-Taxane Regimen

In patients who can tolerate it, use of a regimen containing anthracycline-taxane is considered the optimal strategy for adjuvant chemotherapy, particularly for patients deemed to be at high risk.*

Optimal-Dose Anthracycline Regimen for Patients with High-Risk Breast Cancer Who Will Not Receive a Taxane

For patients with high-risk disease who will not receive a taxane, an optimal-dose anthracycline three-

drug regimen (cumulative dose of doxorubicin ≥240 mg/m^2 or epirubicin ≥600 mg/m^2 but no higher than 720 mg/m^2) that contains cyclophosphamide is recommended. The cumulative dose of doxorubicin in two-drug regimens should not exceed 240 mg/m^2.

ASCO Panel Rationale and Discussion

The Oxford Overview showed that anthracycline-based three-drug regimens, such as six cycles of cyclophosphamide-doxorubicin-fluorouracil (300 mg/m^2 of doxorubicin) or cyclophosphamide-epirubicin-fluorouracil (≥360 mg/m^2 of epirubicin), were superior to cyclophosphamide-methotrexate-fluorouracil. However, studies of anthracycline-based two-drug regimens (versus single-agent paclitaxel) testing a cumulative dose of doxorubicin of more than 240 mg/m^2 in the form of doxorubicin-cyclophosphamide given for six cycles instead of four cycles or for four cycles with a doxorubicin dose of more than 60 mg/m^2 per cycle demonstrated greater toxicity and no improvement in survival. In light of these data, the ASCO Panel modified the CCO recommendation to indicate that the cumulative dose of doxorubicin in two-drug regimens should not exceed 240 mg/m^2.

Adding Gemcitabine or Capecitabine to an Anthracycline-Taxane Regimen

The addition of gemcitabine or capecitabine to an anthracycline-taxane regimen is not recommended for adjuvant chemotherapy.*

Capecitabine in Patients Age 65 Years or Older

In patients age 65 years or older, capecitabine is not recommended as an adjuvant chemotherapy option in lieu of standard regimens such as doxorubicin-cyclophosphamide or cyclophosphamide-methotrexate-fluorouracil (oral cyclophosphamide).

ASCO Panel Rationale and Discussion

The ASCO Panel modified the CCO recommendation to reflect that patients in the clinical trial reported by Muss et al. were age 65 years or older.

Cyclophosphamide-Methotrexate-Fluorouracil as an Alternative to Doxorubicin-Cyclophosphamide

For patients in whom anthracycline-taxane is contraindicated, cyclophosphamide-methotrexate-fluorouracil (with oral cyclophosphamide) is an acceptable chemotherapy alternative to doxorubicin-cyclophosphamide. Of note, the ASCO Panel recommends classic cyclophosphamide-methotrexate-fluorouracil (oral cyclophosphamide days 1 to 14 with intravenous [IV] methotrexate-fluorouracil days 1 and 8, repeated once every 28 days for six cycles) as the default adjuvant cyclophosphamide-methotrexate-fluorouracil regimen. However, the Panel also recognizes that an all-IV cyclophosphamide-methotrexate-fluorouracil regimen once every 21 days is often used in clinical practice and was accepted by some clinical trials (e.g., TAILORx [Trial Assigning Individualized Options for Treatment (Rx)]) on the basis of convenience and tolerability despite the absence of efficacy data from randomized controlled trials.

ASCO Panel Rationale and Discussion

In the Oxford Overview, trials that had controls treated with cyclophosphamide-methotrexate-fluorouracil showed that standard doxorubicin-cyclophosphamide × 4 once every 3 weeks and standard cyclophosphamide-methotrexate-fluorouracil were equivalent. However, single-agent taxane regimens such as paclitaxel given for four or six cycles are not acceptable alternatives because they were not shown to be not inferior to doxorubicin-cyclophosphamide. The ASCO Panel modified the CCO recommendation to include a comment on the use of an all-IV cyclophosphamide-methotrexate-fluorouracil regimen.

Acceptable Adjuvant Chemotherapy Regimens for Patients with Higher-Risk Early-Stage Breast Cancer

These adjuvant chemotherapy regimens can be used for patients with higher-risk early-stage breast

cancer (see also the next recommendation regarding non-anthracycline regimens):

Fluorouracil-epirubicin-cyclophosphamide × 3 → docetaxel × 3 (superior to fluorouracil-epirubicin-cyclophosphamide × 6)
Doxorubicin-cyclophosphamide × 4 → docetaxel × 4 (superior to doxorubicin-cyclophosphamide x 4)
Docetaxel-doxorubicin-cyclophosphamide × 6 (superior to fluorouracil-doxorubicin-cyclophosphamide × 6)
Doxorubicin-cyclophosphamide × 4 → paclitaxel administered once per week
Dose-dense doxorubicin-cyclophosphamide → paclitaxel (once every 2 weeks)

ASCO Panel Rationale and Discussion

The ASCO Panel modified the CCO list of acceptable adjuvant chemotherapy regimens to remove the "dose-dense, dose-intense epirubicin-cyclophosphamide → paclitaxel" regimen because of higher toxicity and lack of overall survival benefit.

Adjuvant Regimen When an Anthracycline Is Not Preferred

Docetaxel-cyclophosphamide × 4 is recommended as an alternative to doxorubicin-cyclophosphamide × 4. Docetaxel-cyclophosphamide offers improved disease-free survival (DFS) and overall survival (OS) compared with four cycles of doxorubicin-cyclophosphamide. Classic cyclophosphamide-methotrexate-fluorouracil with cyclophosphamide for six cycles is another option. Of note, the ASCO Panel recommends classic cyclophosphamide-methotrexate-fluorouracil (oral cyclophosphamide days 1 to 14 with IV methotrexate-fluorouracil days 1 and 8, repeated once every 28 days for six cycles) as the default adjuvant cyclophosphamide-methotrexate-fluorouracil regimen. However, the Panel also recognizes that an all-IV cyclophosphamide-methotrexate-fluorouracil regimen once every 21 days is often used in clinical practice and was accepted by some clinical trials (e.g., TAILORx) on the basis of convenience and tolerability despite the absence of efficacy data from randomized controlled trials.

ASCO Panel Rationale and Discussion

The US Oncology Trial 9735 showed that docetaxel-cyclophosphamide × 4 offers improved DFS and OS when compared with doxorubicin-cyclophosphamide × 4. However, docetaxel-cyclophosphamide × 4 is associated with a higher risk of infection, and use of granulocyte colony-stimulating factor is recommended. Docetaxel-cyclophosphamide × 4 has not been compared against an anthracycline and taxane regimen (in sequence or in combination). Ongoing trials NCT00493870 (Phase III Trial of Taxotere [Docetaxel]-Cytoxan [Cyclophosphamide] [TC] versus taxotere-doxorubicin-cyclophosphamide [TAC] in HER2-Negative Early Stage Breast Cancer Patients), NCT01547741 (Docetaxel and Cyclophosphamide Compared to Anthracycline-Based Chemotherapy in Treating Women with HER2-Negative Breast Cancer), and NCT00887536 (A Clinical Trial Comparing the Combination of TC Plus Bevacizumab to TC Alone and to TAC for Women with Node-Positive or High-Risk Node-Negative, HER2-Negative Breast Cancer) are testing the efficacy (and safety) of docetaxel-cyclophosphamide × six cycles versus three-drug anthracycline- and taxane-containing regimens in high-risk HER2-negative, node-negative or node-positive breast cancer.

The ASCO Panel modified the CCO recommendation to specify that docetaxel-cyclophosphamide should be administered for four cycles and added the statement to the recommendation that, on the basis of the Oxford Overview, cyclophosphamide-methotrexate-fluorouracil for six cycles offers "equivalent" outcomes and is an alternative to doxorubicin-cyclophosphamide once every 3 weeks × 4. The ASCO Panel also modified the CCO recommendation to include a comment on the use of an all-IV cyclophosphamide-methotrexate-fluorouracil regimen.

Recommendations for HER2-Positive Breast Cancer

Patient Selection and Adjuvant Trastuzumab Therapy

Only patients with HER2-positive breast cancer (overexpressed based on immunohistochemistry [3+] or amplified based on in situ hybridization [ratio ≥2.0 or average *HER2* copy number ≥6.0]) should be

offered adjuvant trastuzumab.

ASCO Panel Rationale and Discussion

The ASCO Panel modified the CCO patient selection recommendation slightly from CCO's original language of "6+ HER2 gene copies per cell nucleus" to make this one criterion consistent with the ASCO-College of American Pathologists guideline definition of "positive for HER2" as an average *HER2* gene copy number of ≥6.0 per cell nucleus.

Trastuzumab Plus Chemotherapy in Patients with Higher-Risk HER2-Positive

Trastuzumab plus chemotherapy is recommended for all patients with HER2-positive, node-positive breast cancer and for patients with HER2-positive, node-negative breast cancer tumors (≥1 cm).*

Trastuzumab Plus Chemotherapy in Patients with HER2-Positive T1a-b N0 Disease

Trastuzumab plus chemotherapy may be considered in small (≤1 cm), node-negative tumors.

ASCO Panel Rationale and Discussion

The ASCO Panel adapted the CCO recommendation in light of data published since completion of the CCO guideline to make the recommendation more definitive regarding the use of trastuzumab plus chemotherapy in patients with small, node-negative tumors. There are limited phase III data on the efficacy of trastuzumab in patients with small (≤1 cm), node-negative tumors. In a recent meta-analysis of five of six randomized trials that evaluated the benefit of trastuzumab in tumors ≤2 cm, only 75 patients had T1a-b node-negative disease, but the proportional benefit offered by adjuvant trastuzumab seemed to be the same regardless of tumor size or node status. Two single-arm phase II trials in the node-negative, HER2-positive population suggest an excellent short-term outcome for patients treated with trastuzumab and paclitaxel (49.5% had T1b disease or smaller; two-thirds had estrogen receptor [ER]-positive disease) or with trastuzumab and docetaxel-cyclophosphamide (21.7% of patients had T1b disease or smaller; 64.9% had ER-positive disease). Although data from these single-arm studies are encouraging, they do not support a blanket recommendation for the use of trastuzumab-based chemotherapy for all patients with T1N0 HER2-positive tumors. Historical outcomes suggest excellent outcomes for some patients with T1a-b HER2-positive tumors that were not treated with trastuzumab, particularly those with ER-positive disease treated with optimal endocrine therapy. Therefore, the decision to offer trastuzumab-based chemotherapy for patients with small, node-negative tumors needs to be individualized.

Selection of Chemotherapy Regimens in Patients Receiving Trastuzumab

Trastuzumab can be administered with any acceptable adjuvant chemotherapy regimen.*

Use of Trastuzumab and an Anthracycline-Containing Regimen

The administration of trastuzumab concurrently with the anthracycline component of a chemotherapy regimen is not recommended because of the potential for increased cardiotoxicity.

ASCO Panel Rationale and Discussion

Because of a lack of clinical outcomes benefit and increased cardiotoxicity, concurrent administration of anthracyclines and trastuzumab is not recommended; the ASCO Panel adapted the CCO recommendation to omit the word "generally" from the CCO recommendation.

Concurrent Administration of Adjuvant Trastuzumab and Non-Anthracycline Chemotherapy Regimens

Trastuzumab should be preferentially administered concurrently (not sequentially) with a non-anthracycline chemotherapy regimen.

ASCO Panel Rationale and Discussion

On the basis of data from North Central Cancer Treatment Group NCCTG-N9831 (Combination

Chemotherapy with or without Trastuzumab in Treating Women with HER2-Overexpressing Breast Cancer) trial and on informal panel consensus, the ASCO Panel adapted the CCO recommendation to indicate a preference for concurrent versus sequential administration of trastuzumab and non-anthracycline chemotherapy. One study reported a strong trend toward improved DFS with initiation of trastuzumab concurrent with taxane chemotherapy compared with the sequential administration of taxane followed by trastuzumab once per week for 52 weeks (hazard ratio, 0.77; 99.9% confidence interval [CI], 0.53 to 1.11).

Trastuzumab-Based Chemotherapy/Trastuzumab Regimens for Patients at Higher Risk of Cardiotoxicity

Less cardiotoxicity is seen with docetaxel-carboplatin-trastuzumab than with doxorubicin-cyclophosphamide followed by docetaxel-trastuzumab, and docetaxel-carboplatin-trastuzumab is recommended for patients at higher risk for cardiotoxicity.*

ASCO Panel Rationale and Discussion

Although the efficacy of docetaxel-carboplatin-trastuzumab was not directly tested against doxorubicin-cyclophosphamide followed by docetaxel-trastuzumab in the Breast Cancer International Research Group (BCIRG) 006 (Combination Chemotherapy with or without Trastuzumab in Treating Women with Breast Cancer) trial, lower rates of cardiotoxicity were observed with docetaxel-carboplatin-trastuzumab. These data support preferential use of docetaxel-carboplatin-trastuzumab, particularly for patients who might be at greater risk for cardiac dysfunction, on the basis of factors such as older age, low baseline ejection fraction, and pre-existing hypertension. Of note, BCIRG 006 did not include patients older than age 70 years. Another option for patients with lower-risk node-negative disease who might have a higher risk for cardiotoxicity is trastuzumab-paclitaxel once per week followed by trastuzumab alone on the basis of a single-arm phase II trial in which rates of symptomatic heart failure were low and the observed asymptomatic decreases in ejection fraction improved with trastuzumab interruption and/or cessation.

Addition of Trastuzumab to Chemotherapy Regimens Not Evaluated in a Phase III Trial

No phase III evidence exists for the addition of trastuzumab to some chemotherapy regimens, such as docetaxel-cyclophosphamide. However, those regimens might be in use and are reasonable options, particularly to mitigate cardiotoxicity in certain patients.*

ASCO Panel Rationale and Discussion

Since publication of the CCO guideline, data from two phase II studies have assessed the concomitant administration of taxanes and trastuzumab. The APT (Adjuvant Paclitaxel and Trastuzumab) trial of paclitaxel-trastuzumab once per week for 12 weeks followed by trastuzumab reported excellent short-term (3-year) DFS of 98.7% in a node-negative, lower-risk HER2-positive population. Another phase II study that assessed the concomitant administration of four cycles of docetaxel-cyclophosphamide with trastuzumab followed by trastuzumab alone reported a 3-year DFS of 96.9% for women with early-stage HER2-amplified breast cancer. Given data from these phase II trials and data from the HERA (Herceptin Adjuvant Trial) trial, in which systemic therapy was given per investigator choice, paclitaxel, docetaxel-cyclophosphamide, or any of the regimens used in HERA can be considered a reasonable systemic option in combination with trastuzumab, particularly for patients who are perceived to be at increased risk for cardiotoxicity.

Duration of Trastuzumab Therapy and Cardiac Function Assessment

Patients should be offered 1 year total of adjuvant trastuzumab, with regular assessments of cardiac function during that period.*

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Early invasive breast cancer, including human epidermal growth factor receptor 2 (HER2)-positive and HER2-negative breast cancers

Guideline Category

Management

Risk Assessment

Treatment

Clinical Specialty

Obstetrics and Gynecology

Oncology

Pathology

Intended Users

Advanced Practice Nurses

Nurses

Patients

Physician Assistants

Physicians

Guideline Objective(s)

To present practice recommendations adapted from the Cancer Care Ontario (CCO) Program in Evidence-based Care guideline on the selection of optimal adjuvant chemotherapy regimens for human epidermal growth factor receptor 2 (HER2)-negative and adjuvant targeted therapy for HER2-positive breast cancers

Target Population

Female patients who are being considered for, or who are receiving, systemic therapy after definitive surgery for early-stage invasive breast cancer, defined largely as invasive cancer stages I to IIA (T1N0-1, T2N0)

Interventions and Practices Considered

1. Adjuvant chemotherapy for human epidermal growth factor receptor 2 (HER2)-negative cancers
    - Use of an anthracycline-taxane regimen
    - Optimal-dose anthracycline regimen for patients with high-risk breast cancer who will not receive a taxane

- Adding gemcitabine or capecitabine to an anthracycline-taxane regimen (not recommended)
- Capecitabine in patients 65 years of age and older (not recommended as an adjuvant chemotherapy option in lieu of standard regimens)
- Cyclophosphamide-methotrexate-fluorouracil (CMF) as an alternative to doxorubicin-cyclophosphamide (AC)
- Acceptable adjuvant chemotherapy regimens for patients with higher risk early-stage breast cancer
    - Fluorouracil-epirubicin-cyclophosphamide × 3 → docetaxel × 3
    - Doxorubicin-cyclophosphamide × 4 → docetaxel × 4
    - Docetaxel-doxorubicin-cyclophosphamide × 6
    - Doxorubicin-cyclophosphamide × 4 → paclitaxel administered once per week
    - Dose-dense doxorubicin-cyclophosphamide → paclitaxel (once every 2 weeks)
- Adjuvant regimen when an anthracycline is not preferred
    - Docetaxel-cyclophosphamide × 4
    - Cyclophosphamide-methotrexate-fluorouracil with oral cyclophosphamide × 6
    - Use of an all-intravenous (IV) cyclophosphamide-methotrexate-fluorouracil regimen

2. Adjuvant targeted therapy for HER2-positive cancers
    - Patient selection and adjuvant trastuzumab therapy
    - Trastuzumab plus chemotherapy in patients with higher risk HER2-positive disease
    - Trastuzumab plus chemotherapy in patients with HER2-positive disease if T1a/b N0
    - Selection of chemotherapy regimens in patients receiving trastuzumab
    - Use of trastuzumab and an anthracycline-containing regimen (not recommended)
    - Concurrent administration of adjuvant trastuzumab and non-anthracycline chemotherapy regimens
    - Trastuzumab-based chemotherapy-trastuzumab regimens for patients at higher risk of cardiotoxicity (docetaxel-carboplatin-trastuzumab)
    - Addition of trastuzumab to chemotherapy regimens not evaluated in a phase III trial
    - Duration of trastuzumab therapy and cardiac function assessment

Major Outcomes Considered

- Disease-free survival (DFS)
- Overall survival (OS)
- Adverse effects of treatment

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The adaptation process usually starts with a literature search to identify candidate guidelines for adaptation on a given topic. For this adaptation, however, the target guideline was identified through an informal collaboration between the Cancer Care Ontario (CCO) Program in Evidence-based Care and the American Society of Clinical Oncology (ASCO) guidelines program, which is designed to reduce duplication of effort in oncology practice guideline development across organizations. As part of this collaboration,

CCO guidelines staff made ASCO aware that CCO's comprehensive practice guideline on optimal systemic therapy for early breast cancer in women was nearing completion.

Summary of the CCO Guideline Development Methodology

CCO guideline recommendations were developed by a panel that included experts in medical oncology. The literature searches of MEDLINE and EMBASE that were completed for the broad systematic review spanned the period from January 2008 through March 2012; the search was updated in May 2014. Additional practice guidelines were identified from a search of the SAGE Directory of Cancer Guidelines. Details of the search strategies, the study inclusion criteria, the outcomes of interest, and the search yield are available at the CCO Web site at https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-ebs .

Methods and Results of ASCO Updated Literature Search

A search for new evidence was conducted by ASCO guidelines staff to identify relevant randomized controlled trials, systematic reviews, and meta-analyses published since the CCO guideline was completed. MEDLINE and EMBASE were searched from January 2014 to July 2015 by following the strategies described in the CCO guideline. The search was restricted to articles published in English and to systematic reviews, meta-analyses, and randomized controlled trials. The CCO guideline inclusion criteria were applied to a review of the literature search results. The updated search and review were guided by the signals approach, which is designed to identify only new, potentially practice-changing data—signals that might translate into revised practice recommendations. This approach relied on targeted routine literature searching and the expertise of ASCO Guideline Panel members to help identify potential signals. Panel members also provided additional relevant references from personal files. The Methodology Supplement (see the "Availability of Companion Documents" field) provides additional information about the signals approach. The updated search yielded 4,018 records.

Number of Source Documents

From the 4018 records, 20 potentially relevant abstracts were identified. None of the publications provided new evidence that would warrant substantive modification of the Cancer Care Ontario (CCO) practice recommendations. Two of the publications informed the American Society of Clinical Oncology (ASCO) Panel's comments, and are referenced in the guideline manuscript.

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

Methodologic review of the comprehensive Cancer Care Ontario (CCO) guideline on optimal systemic therapy was completed independently by two American Society of Clinical Oncology (ASCO) guideline staff

members using the Rigour of Development subscale from the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument. Detailed results of the scoring for these assessments are available in the Methodology Supplement (see the "Availability of Companion Documents" field). Overall, the more comprehensive CCO guideline scored 98% in rigor of guideline development.

The content review is completed by an Adaptation Panel convened by ASCO that includes multidisciplinary representation. The Panel members are asked to complete an eight item Guideline Endorsement Content Review Form (see Figure 2 in the Methodology Supplement) that assesses the perceived clarity and clinical utility of the recommendations, and the degree to which the recommendations are consistent with the content reviewers' interpretation of the available data on the topic in question. This form was adapted by ASCO from the Cancer Care Ontario Program in Evidence-based Care Practitioner Feedback instrument.

The Adaptation Panel is led by two Co-Chairs who have the primary responsibility for the development and timely completion of the guideline adaptation. Recommendations from the source guidelines are extracted into a summary matrix.

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

Summary of the Cancer Care Ontario (CCO) Guideline Development Methodology

A working group composed of six medical oncologists and a methodologist drafted guideline recommendations. These draft recommendations were subsequently circulated to the Early Breast Cancer Systemic Therapy Consensus Panel, which included the working group members and 14 additional medical oncologists from Ontario as part of a modified Delphi consensus development technique for which consensus was defined as 80% agreement and no strong disagreement. By using a 5-point point Likert scale (strongly disagree to strongly agree), Consensus Panel members from CCO rated the draft recommendations in advance of a consensus meeting held in November 2012. Selected recommendations for which consensus was not achieved were discussed and voted on at the 2012 consensus meeting.

The American Society of Clinical Oncology (ASCO) Guideline Adaptation Process

This guideline adaptation was informed by the ADAPTE methodology, which was used as an alternative to de novo guideline development. Adaptation of guidelines is considered by ASCO in selected circumstances, when one or more quality guidelines on the same topic from other organizations already exist. The objective of the ADAPTE process (http://www.g-i-n.net/working-groups/adaptation) is to take advantage of existing guidelines to enhance efficient production, reduce duplication, and promote the local uptake of quality guideline recommendations.

ASCO's adaptation process typically begins with a literature search to identify candidate guidelines for adaptation. Adapted guideline manuscripts are reviewed and approved by the ASCO Clinical Practice Guidelines Committee (CPGC). The review includes two parts: methodologic review and content review. The methodologic review is completed by a member of the Clinical Practice Guidelines Committee's Methodology Subcommittee and/or by ASCO senior guideline staff. The content review is completed by an ad hoc panel convened by ASCO that includes representatives of several disciplines. Further details of the methods used for the development of this guideline adaptation are reported in Methodology Supplement (see the "Availability of Companion Documents" field).

Results of Guideline Search and ASCO Topic Priority-Setting Process

On the basis of a preliminary content review of the draft CCO guideline by two members of ASCO's Breast Cancer Advisory Group, the CCO recommendations on the selection of optimal adjuvant chemotherapy

regimens and the selection of adjuvant targeted therapy for human epidermal growth factor receptor 2 (HER2)-positive cancers were selected as a possible adaptation opportunity. The Advisory Group subsequently ranked the adaptation of the CCO recommendations on chemotherapy and targeted therapy as one of its top three priorities for breast cancer guideline development.

Final Recommendations

On the basis of a formal content review of the CCO guideline, the ASCO Panel agreed that, in general, the recommendations were clear and thorough, were based on the most relevant scientific evidence, and presented options that will be acceptable to patients. However, for some topics, the ASCO Panel formulated a set of adapted recommendations on the basis of local context and practice beliefs of the ad hoc panel members and new information.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Final review and approval are completed by the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines Committee (CPGC) after approval by the ASCO Adaptation Panel. The CPGC approved this guideline on January 25, 2016.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Adjuvant chemotherapy improves disease-free survival (DFS) and overall survival (OS) of patients with early breast cancer independent of age, nodal status, and estrogen receptor (ER) status. However, those with triple-negative and human epidermal growth factor receptor 2 (HER2)–positive breast cancer seem to derive the greatest proportional benefit from systemic chemotherapy and biologic therapy.

Potential Harms

- Decisions regarding adjuvant chemotherapy regimens should take into account baseline recurrence risk, toxicities, likelihood of benefit, and host factors such as comorbidities.
- In the Breast Cancer International Research Group (BCIRG) 006 (Combination Chemotherapy with or without Trastuzumab in Treating Women with Breast Cancer) trial, lower rates of cardiotoxicity were observed with docetaxel-carboplatin-trastuzumab than with doxorubicin-cyclophosphamide followed by docetaxel-trastuzumab. These data support preferential use of docetaxel-carboplatin-trastuzumab, particularly for patients who might be at greater risk for cardiac dysfunction, on the basis of factors such as older age, low baseline ejection fraction, and pre-existing hypertension. Another option for patients with lower-risk node-negative disease who might have a higher risk for cardiotoxicity is trastuzumab-paclitaxel once per week followed by trastuzumab alone on the basis of a single-arm phase II trial in which rates of symptomatic heart failure were low and the observed asymptomatic decreases in ejection fraction improved with trastuzumab interruption and/or cessation.

Qualifying Statements

Qualifying Statements

The clinical practice guidelines and other guidance published herein are provided by American Society of Clinical Oncology (ASCO) to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified herein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, because the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicate that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an "as is" basis and makes no warranty, expressed or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

Implementation of the Guideline

Description of Implementation Strategy

For information on the American Society for Clinical Oncology (ASCO) implementation strategy, please see the ASCO Web site .

Implementation Tools

Patient Resources

Quick Reference Guides/Physician Guides

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Denduluri N, Somerfield MR, Eisen A, Holloway JN, Hurria A, King TA, Lyman GH, Partridge AH, Telli ML, Trudeau ME, Wolff AC. Selection of optimal adjuvant chemotherapy regimens for human epidermal growth factor receptor 2 (HER2)-negative and adjuvant targeted therapy for HER2-positive breast cancers: an American Society of Clinical Oncology guideline adaptation of the Cancer Care Ontario clinical practice guideline. J Clin Oncol. 2016 Jul 10;34(20):2416-27. [32 references] PubMed

Adaptation

This guideline is an adaptation of:

> Eisen A, Fletcher GG, Gandhi S, et al: Optimal systemic therapy for early breast cancer in women: a clinical practice guideline. Curr Oncol 22:S67-81, 2015.

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2016 Jul 10

Guideline Developer(s)

American Society of Clinical Oncology - Medical Specialty Society

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American Society of Clinical Oncology

Guideline Committee

Expert Panel for Adaptation of Guideline on Selection of Optimal Adjuvant Chemotherapy Regimens for Early Breast Cancer and Adjuvant Targeted Therapy for Human Epidermal Growth Factor Receptor 2–Positive Breast Cancers

Composition of Group That Authored the Guideline

Panel Members: Neelima Denduluri, MD (*co-chair*), The US Oncology Network, Virginia Cancer Specialists, Arlington, VA; Antonio C. Wolff, MD (*co-chair*), The Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Andrea Eisen, MD, Sunnybrook Health Sciences Centre, and Cancer Care Ontario, Toronto, Ontario, Canada; Jamie N. Holloway, PhD, Patient representative, Arlington, VA; Arti Hurria, MD, City of Hope, Duarte, CA; Tari A. King, MD, Dana-Farber/Brigham and Women's Cancer Center, Boston, MA; Gary H. Lyman, MD, MPH, Fred Hutchinson Cancer Research Center, Seattle, WA; Ann H. Partridge, MD, Dana-Farber Cancer Institute, Boston, MA; Melinda L. Telli, MD, Stanford University, Palo Alto, CA; Maureen E. Trudeau, MD, MA, Sunnybrook Health Sciences Centre, and Cancer Care Ontario, Toronto, Ontario, Canada

Financial Disclosures/Conflicts of Interest

The Expert Panel was assembled in accordance with American Society of Clinical Oncology's (ASCO's) Conflict of Interest Policy Implementation for Clinical Practice Guidelines (http://www.asco.org/rwc). All members of the Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria; consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the Panel members did not disclose any relationships constituting a conflict under the Policy.

Authors' Disclosures of Potential Conflicts of Interest

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Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Journal of Clinical Oncology Web site .

Availability of Companion Documents

The following are available:

- Selection of optimal adjuvant chemotherapy regimens for human epidermal growth factor receptor 2 (HER2)-negative and adjuvant targeted therapy for HER2-positive breast cancers: an American Society of Clinical Oncology guideline adaptation of the Cancer Care Ontario clinical practice guideline. Methodology supplement. Alexandria (VA): American Society of Clinical Oncology; 2016. 17 p. Available from the Journal of Clinical Oncology Web site .
- Selection of optimal adjuvant chemotherapy regimens for human epidermal growth factor receptor 2 (HER2)-negative and adjuvant targeted therapy for HER2-positive breast cancers: an American Society of Clinical Oncology guideline adaptation of the Cancer Care Ontario clinical practice guideline. Data supplement. Alexandria (VA): American Society of Clinical Oncology; 2016. 6 p. Available from the Journal of Clinical Oncology Web site .
- Selection of optimal adjuvant chemotherapy regimens for human epidermal growth factor receptor 2 (HER2)-negative and adjuvant targeted therapy for HER2-positive breast cancers: an American Society of Clinical Oncology guideline adaptation of the Cancer Care Ontario clinical practice guideline. Slide set. Alexandria (VA): American Society of Clinical Oncology; 2016. 18 p. Available

from the American Society of Clinical Oncology (ASCO) Web site .

Selection of optimal adjuvant chemotherapy regimens for human epidermal growth factor receptor 2 (HER2)-negative and adjuvant targeted therapy for HER2-positive breast cancers: an American Society of Clinical Oncology guideline adaptation of the Cancer Care Ontario clinical practice guideline. Summary of recommendations table. Alexandria (VA): American Society of Clinical Oncology; 2016. 4 p. Available from the ASCO Web site .

Patient Resources

The following is available:

Breast cancer. Treatment options. Available from the Cancer.Net Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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